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Asymmetric Synthesis of Both the Enantiomers of *trans*-3-Hydroxypipecolic Acid†

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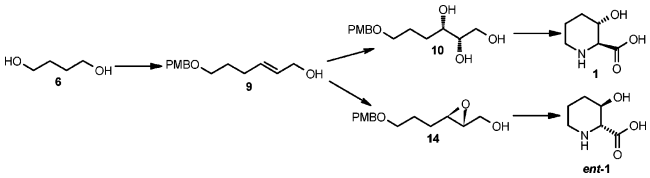

Both the enantiomers of *trans*-3-hydroxypipecolic acid have been synthesized employing the Sharpless asymmetric dihydroxylation and epoxidation as the key steps starting from a commercially available starting material 1,4-butanediol.

Functionalized piperidines are among the most ubiquitous heterocyclic building blocks in natural products and synthetic compounds with important activities. Therefore, a huge amount of synthetic effort has been put on the preparation of these systems.[1] Hydroxylated piperidine alkaloids are frequently found in living systems and display a wide range of biological activities due to their ability to mimic carbohydrate substrates in a variety of enzymatic processes.[2] Selective inhibition of a number of enzymes involved in the binding and processing of glycoproteins has rendered piperidine alkaloids important tools in the study of biochemical pathways.[3] 3-Hydroxypipecolic acids **1** and **2**, six-membered cyclic α-amino-*β*-hydroxy acids, constitute non-natural variants of a structural motif often encountered in a variety of functional molecules and may be regarded as expanded hydroxylated proline or a conformationally restricted serine derivative and may affect the physiological and pathological processes.[4] The piperidine unit of 3-hydroxypipecolic acid is found in a number of biologically important products. For example, the *cis*-isomer **2** forms a part of the structure of tetrazomine **3**, an antitumor antibiotic,[5] while the *trans* isomer **1** is a precursor of (−)-swainsonine **4**, which has shown potent and specific α-D-mannosidase inhibitory activity,[6] and it is also found in the structure of febrifugine **5**, a potent antimalarial agent[7] (Figure 1).

As a consequence, a practical route providing an easy access to the title compounds should be highly desirable, also considering that these compounds might be precious scaffolds to be incorporated into conformationally restricted peptidomimetics of biological relevance.

From a synthetic point of view, only a few enantioselective synthesis of **1** or its isomers have been reported. While the majority of their earlier syntheses utilize either chiral pool as starting material[5−8] or the enzymatic resolution,[9] reports in which all the stereogenic centers are constructed by asymmetric synthesis are rather scarce.[10] Despite recent improvements in the synthetic methodology for the control of the two stereocenters in the target molecule **1**, most of them suffer either from poor diastereoselectivity, low overall yields, and/or a large number of steps involved. As a part of our research program aimed at developing enantioselective syntheses of naturally occurring amino alcohols,[11] we became interested in developing a simple and feasible route to *trans*-3-hydroxypipecolic acid. Herein we wish to report a new and highly enantioselective synthesis of **1** employing the Sharpless asymmetric dihydroxylation and epoxidation as the source of chirality.

The synthesis of the target compound **1** commenced from the allylic alcohol **9** which in turn could be easily derived from a commercially available starting material 1,4-butanediol. Thus, as illustrated in Scheme 1, 1,4-butanediol **6** was treated with *p*-methoxybenzyl bromide

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† Dedicated to Professor Hiriyakkanavar Ila on the occasion of her 60th birthday.

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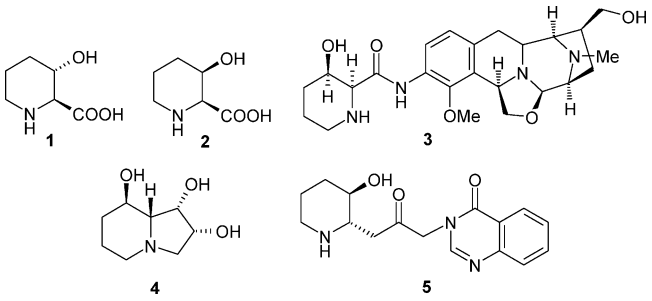
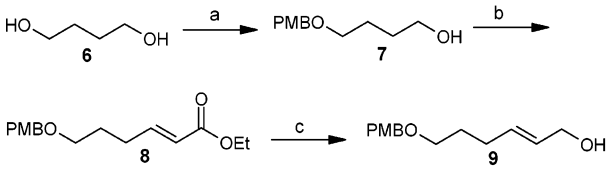


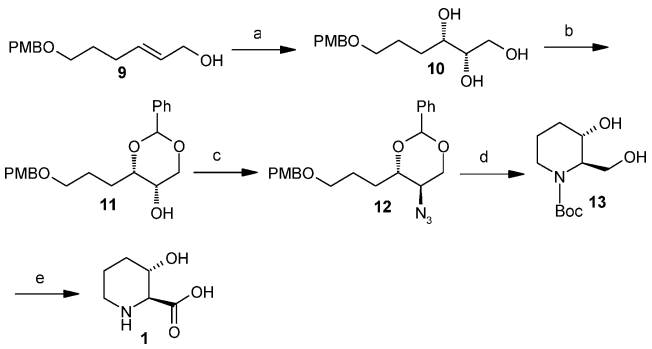
FIGURE 1. Structures of *trans*- and *cis*-3-hydroxypipecolic acid, **1** and **2,** tetrazomine **3**, (−)-swainsonine **4**, and febrifugine **5**.

SCHEME 1[a]



[a] Reagents and conditions: (a) DMF, NaH, *p*-OMeC$_6$H$_4$CH$_2$Br, 80%; (b) (i) PCC, NaOAc, Celite, CH_2Cl_2, 6 h, rt, (ii) Ph_3P=$CHCO_2Et$, benzene, reflux 4 h, 80%; (c) DIBAL-H, CH_2Cl_2, rt, 1 h, 80%.

SCHEME 2[a]



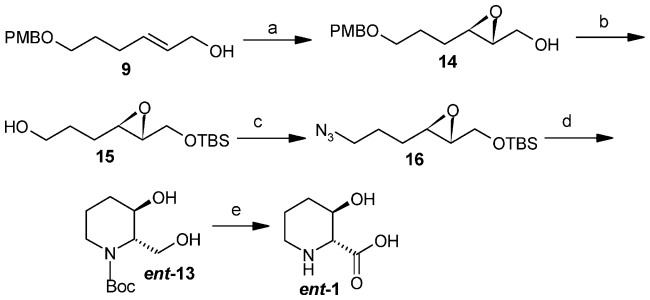
[a] Reagents and conditions: (a) K_2CO_3, K_3FeCN_6, $CH_3SO_2NH_2$, $(DHQ)_2PHAL$ (1 mol %), 0.1 M OsO_4 (0.4 mol %), *t*-BuOH/H_2O (1:1), 0 °C, 18 h, 71%; (b) $C_6H_5CH(OMe)_2$, CH_2Cl_2, TsOH, rt, 85%; (c) (i) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, (ii) NaN_3, DMF, 80 °C, 24 h, 80%; (d) (i) DDQ, CH_2Cl_2, H_2O, 3 h, rt, (ii) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, (iii) H_2/10% Pd−C, MeOH, 30 h, then Boc_2O, 59%, three steps; (e) ref 7.

in the presence of NaH to give **7** in 80% yield. The alcohol **7** was subjected to PCC oxidation followed by two carbon homologation using Wittig reaction to afford the α,β-unsaturated ester **8** in excellent yield. The ester **8** was reduced with DIBAL-H to furnish the corresponding allylic alcohol **9** in 80% yield.

Scheme 2 summarizes the synthesis of target compound **1** from the allylic alcohol **9**. Thus, the dihydroxylation of olefin **9** with osmium tetraoxide and potassium ferricyanide as co-oxidant in the presence of 1,4-bis-(dihydroquinin-9-*O*-yl)phthalazine [$(DHQ)_2PHAL$] ligand under the Sharpless asymmetric dihydroxylation reaction conditions[12] gave the (2S,3S)-triol **10** in 71% yield and 92% ee.[13]

Furthermore in order to achieve the synthesis of 3-hydroxypipecolic acid **1** from the triol **10**, we required

SCHEME 3[a]



[a] Reagents and conditions: (a) Ti(*i*-OPr)$_4$, (−)-DIPT, TBHP, CH_2Cl_2, −20 °C, 20 h, 67%; (b) (i) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 10 h, rt, (ii) DDQ, CH_2Cl_2, H_2O, 3 h, rt, 90%, two steps; (c) (i) MsCl, Et_3N, CH_2Cl_2, rt, (ii) NaN_3, DMF, 70 °C, 82%, two steps; (d) Ph_3P, THF/H_2O (1:1), rt, 48 h; then Boc_2O, NaOH; TBAF, THF, rt, 1 h, 48%; (e) ref 7.

the transformation of a hydroxy group into an azido one, with concomitant reversal of stereochemistry at the 2-position. To this end, protection of **10** as a benzylidene derivative was effected using benzaldehyde dimethyl acetal in the presence of a catalytic amount of *p*-TSA to afford a mixture of 1,3- and 1,2-benzylidene compound in 9:1 ratio. The desired major 1,3-benzylidene compound **11** was separated by silica gel column chromatography. Compound **11** was then converted into *O*-mesylate derivative which on reaction with sodium azide in DMF afforded compound **12** with the desired stereochemistry at the 5-position. The *p*-methoxybenzyl protecting group was cleaved by treating **12** with DDQ. The free hydroxyl group thus obtained was mesylated and subjected to the reductive ring closure, cleavage of benzylidene group and in situ Boc protection of the free amine to afford 4-deoxyfagomine **13** in overall 59% yield. Transformation of compound **13** into the target molecule **1** was readily accomplished by the Boc deprotection and subsequent oxidation of primary alcohol into the acid using the literature method.[7]

In an alternative strategy to the synthesis of the target molecule **1**, the Sharpless asymmetric epoxidation of **9** was employed as the key step (Scheme 3). Thus, the allylic alcohol **9** was treated with titanium tetraisopropoxide and *tert*-butyl hydroperoxide in the presence of (−)-DIPT under the Sharpless asymmetric epoxidation reaction conditions[14] to give the enantiomerically enriched epoxide **14**[15] in 67% yield.

The subsequent *tert*-butyldimethylsilyl protection of the hydroxyl group followed by deprotection of the *p*-methoxybenzyl group with DDQ gave the desired compound **15** in 90% yield. The free hydroxyl group of **15** was then mesylated and subjected to nucleophilic

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(13) The enantiomeric excess was determined by converting the free secondary hydroxyl group of compound **11** into its Mosher's derivative and analyzing the ^{19}F NMR spectrum. The ee was found to be 92%.

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azide displacement to furnish the azido compound **16** in 82% yield. The azide **16** was treated with triphenylphosphine in the presence of water, resulting in its reduction to amine followed by subsequent epoxide ring opening by amine and in situ cyclization and Boc protection to afford deoxyfagomine *ent*-**13** in 48% yield. As expected, only the product derived from a 6-endo-tet cyclization was detected, and this observation was found to be in accord with those reported.[16] The subsequent conversion to the target compound *ent*-**1** is already reported in the literature.[7] Thus, the merits of this synthesis are ready access to the required stereogenic centers, high enantioselectivity and various possibilities available for structural modification. A short reaction sequence and high overall yield of the target compound render our strategy a good alternative to the known methods.

In summary, a practical and enantioselective synthesis of (2*S*,3*S*)- and (2*R*,3*R*)-3-hydroxypipecolic acid has been achieved using Sharpless asymmetric dihydroxylation and epoxidation. To the best of our knowledge, this is the first asymmetric synthesis of 3-hydroxypipecolic acid using Sharpless asymmetric dihydroxylation and epoxidation as the source of chirality. The synthetic strategy described has significant potential for further extension to other isomers and related analogues. Currently studies are in progress in this direction.

Experimental Section

(2*S*,3*S*)-6-(4-Methoxybenzyloxy)hexane-1,2,3-triol (10). To a mixture of $K_3Fe(CN)_6$ (8.37 g, 25.44 mmol), K_2CO_3 (3.51 g, 25.44 mmol), and $(DHQ)_2PHAL$ (66 mg, 1 mol %, 0.085 mmol) in *tert*-butyl alcohol/H_2O (1:1, 100 mmol) at 0 °C was added OsO_4 (0.1 M solution in toluene, 0.64 mL, 0.4 mol %), followed by methanesulfonamide (0.805 g, 8.47 mmol). After being stirred for 2 min at 0 °C, the allylic alcohol **9** (2.0 g, 8.47 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 18 h and then quenched with sodium sulfite (4 g). The stirring was continued for an additional 30 min, and then the solution was extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with 10% KOH and brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:7) as eluent gave the triol **10** (1.6 g, 71%) as thick liquid. $[\alpha]^{20}_D$: −5.3 (*c* 0.84, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): ν_{max} 3018, 3389. ^1H NMR (300 MHz, $CDCl_3$): 1.62−1.78 (m, 4H), 3.07 (brs, 3H), 3.48−3.54 (m, 2H), 3.67−3.71 (m, 4H), 4.46 (s, 2H), 6.88 (d, 2H, J = 9 Hz), 7.26 (d, 2H, J = 9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.8, 30.0, 55.0 63.9, 69.9, 71.4, 72.2, 74.1, 113.5, 129.2, 129.0, 158.9. MS (ESI): 270(M^+), 234, 142, 91. Anal. Calcd for $C_{14}H_{22}0_5$: C, 62.20; H, 8.20. Found: C, 62.28; H, 8.45.

(2*S*,3*S*)-4-[3-(4-Methoxybenzyloxy)propyl]2-phenyl-1,3-dioxan-5-ol (11). To a solution of triol **10** (1.5 g, 5.56 mmol) in dry CH_2Cl_2 (80 mL) were added *p*-TsOH (150 mg) and benzaldehyde dimethyl acetal (1.02 g, 6.7 mmol). The reaction mixture was stirred at room temperature overnight. Subsequently, it was neutralized with satd aq $NaHCO_3$ (20 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with aq $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent afforded 1,3-protected alcohol **11**, the major product (1.55 g, 85%) as pale yellow thick liquid. $[\alpha]^{20}_D$:−7.4 (*c* 0. 4, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): ν_{max} 1247, 1512, 1612, 1713, 2857, 2933, 3452. ^1H NMR (500 MHz, $CDCl_3$): δ 1.75−1.89 (m, 4H), 3.49−3.54 (m, 3H), 3.82 (s, 3H), 3.83 (m, 2H), 3.84−3.88 (m, 1H), 4.04−4.26 (m, 1H), 4.46 (s, 2H), 5.56 (s, 1H), 6.89 (d, 2H, J = 9 Hz), 7.28 (d, 2H, J = 9 Hz), 7.39 (t, 3H, J = 8 Hz), 7.51 (d, 2H, J = 9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.0, 27.7, 54.9, 65.0, 69.6, 72.3, 79.5, 100.9, 113.6, 125.8, 127.9, 128.5, 129.0, 130.1, 159.0. MS (ESI): 376 ($M + NH_4^+$), 316, 279, 237, 183. Anal. Calcd for $C_{21}H_{26}0_5$: C, 70.37; H, 7.31. Found: C, 70.31; H, 7.35.

(2*R*,3*S*)-5-Azido-4-[3-(4-methoxybenzyloxy)propyl]-2-phenyl-1,3-dioxane (12). To a solution of 1,3-protected alcohol **11** (1.0 g, 2.79 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C were added methanesulfonyl chloride (0.48 g, 4.2 mmol), Et_3N (0.57 g, 5.63 mmol), and DMAP (cat.). The reaction mixture was stirred at room temperature overnight and then poured into an $Et_2O{\cdot}H_2O$ mixture. The organic phase was separated and the aqueous phase extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to a yellow syrupy liquid, which was used as such in the next step.

To the solution of above mesylate in dry DMF (30 mL) was added sodium azide (1.36 g, 20.95 mmol), and the reaction mixture was stirred at 80 °C for 24 h. It was then cooled, poured into water, and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent furnished the azide **12** (0.86 g, 80%) as pale yellow oil. $[\alpha]^{20}_D$: −6.3 (*c* 1.32, $CHCl_3$). IR. ($CHCl_3$, cm^{-1}): ν_{max} 2100, 2882, 2940, 3338. ^1H NMR (500 MHz, $CDCl_3$): 1.72−1.89 (m, 4H), 3.42−3.56 (m, 4H), 3.73 (s, 3H), 3.75−3.98 (m, 1H), 4.18−4.24 (m, 1H), 4.46 (s, 2H), 5.57 (s, 1H), 6.89 (d, 2H, J = 9 Hz), 7.26−7.28 (m, 2H), 7.40 (t, 3H, J = 9 Hz), 7.50 (d, 2H, J = 9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.2, 27.6, 29.3, 51.6, 55.0, 63.4, 66.8, 69.0, 72.4, 78.0, 103.9, 113.7, 126.3, 128.2, 129.1, 129.3, 130.4. MS (ESI): 383 (M^+), 370, 356, 279, 234, 204, 161, 149. Anal. Calcd for $C_{21}H_{25}N_30_4$: C, 65.78; H, 6.57; N, 10.96. Found: C, 65.84; H, 6.55; N, 11.02.

(2*R*,3*S*)-3-Hydroxy-2-hydroxymethylpiperidine-1-carboxylic Acid *tert*-Butyl Ester (13). To a solution of azide **12** (1.0 g, 2.61 mmol) in CH_2Cl_2 (30 mL) and H_2O (1.2 mL) at 0 °C was added DDQ (0.652 g, 2.87 mmol) in portions. The resultant mixture was stirred at room temperature for 3 h, and then satd aq $NaHCO_3$ (10 mL) was added. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (6:4) as eluent afforded the azido alcohol (0.62 g, 90%) as a pale yellow oil.

To a solution of azido alcohol (0.5 g, 1.90 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C were added methanesulfonyl chloride (0.33 g, 2.89 mmol), Et_3N (0.385 g, 3.8 mmol), and DMAP (cat.). The reaction mixture was stirred at room temperature overnight and then poured into the $Et_2O{\cdot}H_2O$ mixture. The organic phase was separated and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated to a syrupy liquid, which was used as such in the next step.

To the solution of above mesylate in methanol was added 10% Pd/C (10 w/w, 80 mg). The reaction mixture was stirred for 30 h under H_2 (1 atm.), *tert*-butyl dicarbonate (0.54 g, 2.47 mmol) was added to the resultant mixture, and stirring was continued for an additional 12 h. The reaction mixture was filtered through a Celite pad and the filtrate concentrated. Silica gel column chromatography of the residue using $CHCl_3$/MeOH (19:1) as eluent furnished deoxyfagomine **13** (0.255 g, 59%) as thick syrupy liquid. $[\alpha]^{25}_D$: +5.2 (*c* 0.25, MeOH). IR ($CHCl_3$, cm^{-1}): ν_{max} 1675, 2854, 2987, 3359, 3478. ^1H NMR (500 MHz, $CDCl_3$ + $DMSOD_6$): δ 1.46 (s, 9H), 1.73−1.81 (m, 4H), 2.98−3.01 (m, 1H), 3.32−3.38 (m, 1H), 3.45−3.53 (m, 1H), 3.67−3.71 (m, 2H), 3.91−3.95 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$ + $DMSOD_6$): δ 20.1, 28.6, 29.2, 32.6, 42.1, 62.3, 64.0, 80.8, 156.5. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.23; H, 9.18; N, 6.27.

(2*R*,3*R*)-{3-[3-(4-Methoxybenzyloxy)propyl]oxiranyl}-methanol (14). To a solution of Ti(O*i*-Pr)$_4$ (4.33 g, 5.25 mmol) in CH_2Cl_2 (40 mL) at −20 °C was added (−)-DIPT (4.47 g, 19.08

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mmol). After the mixture was stirred for 10 min, allylic alcohol **9** (3.0 g, 12.71 mmol) was added. After the mixture was stirred for 20 min at −20 °C, *t*-BuOOH (5.0 M in decane, 5.1 mL, 2.292 g, 25.43 mmol) was added and the reaction mixture was stirred for 20 h at −20 °C. The resultant mixture was then quenched by addition of satd aq $NaHCO_3$ (40 mL) and Et_2O (80 mL). The resultant mixture was stirred for 1 h at room temperature after which it was filtered through a pad of Celite. The filtrate was diluted with Et_2O (80 mL) and stirred for 20 min with 1 M NaOH (50 mL). The phases were separated, and the aqueous phase was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluent afforded the epoxide **14** (2.1 g, 67%) as a colorless oil. $[\alpha]^{20}_D$: +21.5 (*c* 1, $CHCl_3$) [lit.[15] $[\alpha]^{29}_D$: +21 (*c* 2.2, $CHCl_3$)]. IR ($CHCl_3$, cm^{-1}): ν_{max} 1578, 1684, 2856, 2924, 3458. ^1H NMR (500 MHz, $CDCl_3$): δ 1.76−2.05 (m, 4H), 3.47 (q, 2H, J = 5 Hz), 3.68−3.78 (m, 2H), 3.81 (s, 3H), 3.86 (q, 1H, J = 10 Hz), 3.95 (q, 1H, J = 5 Hz), 4.60 (s, 2H), 6.89 (d, 2H, J = 10 Hz), 7.28 (d, 2H, J = 10 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.5, 27.5, 54.8, 62.0, 67.9, 72.0, 80.4, 113.7, 129.2, 130.4, 131.7, 158.9. MS (ESI): 252 (M^+), 230, 200, 121. Anal. Calcd for $C_{14}H_{20}0_4$: C, 66.65; H, 7.99. Found: C, 66.60; H, 8.00.

(2*R*,3*R*)-3-[3-*(tert*-Butyldimethylsilanyloxymethyl)-oxiranyl]propan-1-ol (15). To an ice-cold solution of Et_3N (1.45 g, 14.33 mmol) in CH_2Cl_2 (40 mL) were added DMAP (cat.) and TBDMSCl (1.8 g, 11.94 mmol). After 5 min, the epoxide **14** (2.0 g, 7.94 mmol) in CH_2Cl_2 (10 mL) was added. The resultant mixture was stirred at room temperature for 10 h and then poured into satd aq $NaHCO_3$, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography using petroleum ether/EtOAc (9:1) furnished the TBS-protected epoxide (2.61 g, 90%) as a colorless oil.

To a solution of TBS-protected epoxide (2.0 g, 5.46 mmol) in CH_2Cl_2 (40 mL) and H_2O (2.0 mL) at 0 °C was added DDQ (1.364 g, 60.08 mmol) in portions. The resultant mixture was stirred at room temperature for 3 h, and then satd aq $NaHCO_3$ (10 mL) was added. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the residue using petroleum ether/EtOAc (3:1) as eluent furnished the alcohol **15** (1.21 g, 90%) as a pale yellow oil. $[\alpha]^{20}_D$: + 13.9 (*c* 0.46, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): ν_{max} 1604, 1686, 2874, 2932, 3412. ^1H NMR (500 MHz, $CDCl_3$): δ 0.08 (s, 6 H), 0.90 (s, 9 H), 1.89−1.97 (m, 4H), 3.21 (brs, 1H), 3.60−3.85 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.7, 18.0, 25.5, 25.6, 26.8, 64.5, 68.0, 73.0, 78.9. MS (ESI): 264 ($M + NH_4^+$), 254, 230, 200, 121. Anal. Calcd for $C_{12}H_{26}0_3Si$: C, 58.49; H, 10.63; Si, 11.40. Found: C, 58.52; H, 10.59; Si, 11.30.

(2*R*,3*R*)-[3-(3-Azidopropyl)oxiranyl]methanol (16). To a solution of epoxide **15** (0.750 g, 3.05 mmol) in CH_2Cl_2 (30 mL) at 0 °C were added Et_3N (0.617 g, 6.09 mmol) and methanesulfonyl chloride (0.524 g, 4.574 mmol). The resultant mixture was stirred overnight at room temperature and the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to a yellow oil that was used as such for the next step.

To the solution of the above mesylate in dry DMF (20 mL) was added sodium azide (1.0 g, 15.4 mmol), and the reaction mixture was stirred at 70 °C overnight. The solution was cooled to room temperature and then poured into $Et_2O{\cdot}H_2O$ (50 mL 1:1). The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with H_2O and brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the residue using petroleum ether/EtOAc (7:3) afforded the azido epoxide **16** (0.9 g, 82%) as a pale yellow oil. $[\alpha]^{20}_D$: +11.2 (*c* 0.4, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): ν_{max} 1225, 1347, 2100, 2836, 2953. ^1H NMR (500 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.90 (s, 9H), 1.72−2.07 (m, 4H), 3.48−3.49 (m, 2H) 3.79 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.7, 18.0, 25.5, 26.2, 28.9, 52.4, 64.5, 68.8, 79.1.

(2*S*,3*R*)-3-Hydroxy-2-hydroxymethylpiperidine-1-carboxylic Acid *tert*-Butyl Ester (*ent*-13). To a solution of azido epoxide **16** (0.500 g, 1.84 mmol) in THF (9 mL) and H_2O (1 mL) was added triphenylphosphine (0.73 g, 2.78 mmol). The reaction mixture was stirred at room temperature for 48 h after which *tert*-butyl dicarbonate (0.48 g, 2.21 mmol) and sodium hydroxide (0.09 g, 2.25 mmol) were added and the stirring was continued for additional 12 h. The reaction mixture was neutralized by addition of 10% solution of $KHSO_4$ and diluted with CH_2Cl_2. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. To this crude product in THF (10 mL) was added TBAF (0.8 mL, 1.0 M in THF) and the reaction mixture stirred for 1 h at room temperature. TLC analysis at this point indicated the deprotection of the TBDMS group. The reaction was quenched with aq satd NH_4Cl (5 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (4 × 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the residue using $CHCl_3$/MeOH (19:1) as eluent afforded the cyclized product *ent*-**13** (0.2 g, 48%) as thick syrupy liquid. $[\alpha]^{20}_D$: −5.2 (*c* 0.25, MeOH). Spectroscopic data obtained is same as that of compound **13**.

(2*S*,3*S*)-3-Hydroxypipecolic Acid (1). Mp: 232−236 °C (lit.[8a] mp 230−238 °C). $[\alpha]^{20}_D$: +13.5 (*c* 0.2, 10% aq HCl) [lit.[8a] $[\alpha]^{20}_D$ +12.9 (*c* 0.23, 10% aq HCl)]. IR ($CHCl_3$, cm^{-1}): 2500, 2846, 2983, 3364. ^1H NMR (200 MHz, D_2O): δ 1.62−1.66 (m, 2H), 1.89−1.93(m. 2H), 2.84−2.99 (m, 1H), 3.82−3.83 (m, 1H), 4.10−4.15 (m, 1H), 4.32(brs, 1H). ^{13}C NMR (50 MHz, D_2O): δ 20.1, 29.9, 46.4, 62.0, 66.4, 176.4.

(**2*R*,3*R*)-3-Hydroxypipecolic Acid (*ent*-1).** Mp: 235−239 °C [lit.[8a] mp 234−239 °C]. $[\alpha]^{20}_D$: −13.5 (*c* 0.2, 10% aq HCl) [lit.[8a] $[\alpha]^{20}_D$ −13.0 (*c* 0.2, 10% aq HCl)].

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Supporting Information Available: Spectroscopic data and full experimental procedure for compounds **7**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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